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Research article

Maternal swimming exercise during pregnancy attenuates anxiety/depressive-like behaviors and voluntary morphine consumption in the pubertal male and female rat offspring born from morphine dependent mothers

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ABSTRACT

This study was designed to examine whether maternal swimming exercise during pregnancy would attenuate prenatally morphine-induced anxiety, depression and voluntary consumption of morphine in the pubertal male and female rat offspring. Pregnant rats during the development of morphine dependence were allowed to swim (30–45 min/d, 3 days per a week) on gestational days 11–18. Then, the pubertal male and female rat offspring were tested for the elevated plus-maze (EPM), sucrose preference test (SPT) and voluntary morphine consumption using a two-bottle choice (TBC) paradigm. The results showed that male and female rat offspring born of the swimmer morphine-dependent mothers exhibited an increase in EPM open arm time and entries, higher levels of sucrose preference than their sedentary control mothers. Voluntary consumption of morphine was less in the male and female rat offspring born of the swimmer morphine-dependent mothers as compared with their sedentary control mothers during three periods of the intake of drug. Thus, swimming exercise in pregnant morphine dependent mothers decreased anxiety, depressive-like behavior and also the voluntary morphine consumption in the pubertal male and female offspring, which may prevent prenatally morphine-induced behavioral sensitization in offspring.

1. Introduction

Prenatal morphine exposure can cause developmental delay in the fetal cerebrum [17] neurobehavioral deficits in offspring such as morphine tolerance [5], morphine-induced conditioned place preference (CPP) and behavioral sensitization [24], vulnerability to drug abuse in future generations [22], the anxiety [9], depressive [10]-like behavior, voluntary consumption of morphine [9]. It has shown that prenatal morphine exposure on gestational days 11–18 alter the development of brain systems that involved in reward and motivation- related behaviors [22,23].

We have already observed that voluntary exercise during chronic oral administration of morphine in pregnant rats decreases the anxiety-like behavior and voluntary consumption of morphine in male offspring [9]. It has been shown that maternal exercise during pregnancy enhanced short-term memory, hippocampal neurogenesis [11], antioxidant activity and mitochondriogenesis in brain [13], spatial learning acquisition [3], and decreased anxiety [4] of rat offspring. Moreover, we have previously observed that regular swimming exercise reduces the severity of physical and psychological dependence and voluntary morphine consumption in morphine-dependent and withdrawn rats [7] and morphine-induced reward and behavioral sensitization in maternally-separated rat offspring [1]. Swimming might be one of the most suitable exercises during the gestational period [12] to activation of antioxidant mechanisms under thermal stress [15], with no harm to the fetus [12]. On the other hand, the effect of exercise during pregnancy in morphine dependent rat mothers has been less studied. Given the well-known beneficial effects of swimming exercise, the aim of the present study was to investigate whether regular swimming exercise as forced exercise during induction of morphine dependence on gestational days 11–18 would attenuate prenatally morphine-induced anxiety/depressive-like behaviors and voluntary morphine

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consumption in the pubertal male and female rat offspring.

2. Materials and methods

2.1. Animals and induction of morphine dependence

Male Wistar rats (250 ± 10 g, n = 16) were allowed to mate with female virgin Wistar rats (250 ± 10 g, n = 16) during a 24 h period. Observation of vaginal plug was considered as gestational day 0 (G0) [9]. Then, pregnant rats were randomly divided into four groups of control-sedentary (Cont/No Swim), control −swimming exercise (Cont/Swim), morphine dependent- sedentary (D/No Swim), morphine dependent-swimming exercise (D/Swim), and were housed individually in cages with a 12 h light/dark cycle at 22–24 °C temperature. Food and water were available ad libitum. All of the experimental procedures were conducted in accordance with the National Institutes of Health's Guide for the Care and Use of Laboratory Animals (were approved by University Ethics Committee). Pregnant rats were made dependent with subcutaneous injections of morphine sulphate (Temad Company, Iran) twice per day at 12 h intervals (06:00 and 18:00 h) in the presence or absence of swimming exercise (see below) on gestational days 11–18 (GD11-18). The initial morphine dose was 5 mg/kg for 3 days; thereafter through day 18, rats received 10 mg/kg of morphine [16,23]. A gradual reduction in doses of morphine was continued for 4 days later (7, 5, 3 and 1 mg/kg, respectively) in order to avoid the effect of morphine withdrawal on labor and lactation [9]. Naloxone-precipitated morphine withdrawal signs were observed in sedentary morphine-dependent mothers those offspring were born dead (n = 2) (data not shown). Control rats were treated similarly, except that normal saline was used. Postnatal 0 (PND 0) was the day of birth. The offspring were weaned at 21 days of birth (PND 21) and housed together in their cages with same-sex littermates up to puberty. To exclude any possible effects of prenatal factors, one or two pups of each sex from each litter randomly assigned for each group. The offspring (n = 8/sex/group) were randomly divided into four groups according to sex, as mentioned above. All behavioral tests were performed in PND35 to PND50 (14 days after the weaning to avoid the stress of weaning) during puberty of male and female offspring, because of dramatic transitions in stress reactivity during pubertal development (see Fig. 1. timelines of experiments).

2.2. Regular swimming exercise

Swimming pool was a blue circular pool (140 cm in diameter and 50 cm high) filled to a 25 cm depth with 31 ± 1 °C water. To acclimate to the new environment, swimmer pregnant rats were adapted to water before beginning the experiment on gestational days 7–10. First, rats were placed for 5 min into the swimming pool with shallow water only for standing. At the second day, rats spent 5 min in head-high water in order to start of the swim. At the third day, the water was deep enough, so they had to swim for 5 min. At the fourth day of adaptation, the rats had to swim for 15 min. The training period was gradually and progressively increased for 30 min on the first until 45 min on the last day (on gestational day 18). Rats were rested once every 3 days, as described previously [7,14] (Fig. 1).

2.3. Anxiety measurement in the EPM (elevated plus maze)

To assess the level of anxiety, the rat offspring (PND 35) were individually placed in the center of the EPM with two open (50 cm × 10 cm) and closed (50 cm × 10 cm × 40 cm) arms, and a central platform(10 cm × 10 cm), and allowed to explore the apparatus for 5 min. Time spent in, and entries into open and closed arms were measured by a tracking system (EthoVision, Noldus, The Netherlands) during each 5 min test, as we described previously [9].

2.4. Sucrose preference test (SPT)

To assess the level of anhedonia, each rat was housed individually in cages for 24 h before testing (PND 36) to reduce stress. The rat offspring (PND 37-38) were allowed access to two bottles in each cage for 48 h, one with 200 ml of 32% sucrose (w/v) and the other also with 200 ml of tap water. The positions of the bottles were changed every 12 h to prevent learning. Fluid intake and sucrose were measured every day. At the end of 48 h, the bottles were removed and sucrose preference was calculated as: 100% × sucrose solution consumption (ml)/total fluid consumption (ml), as we described previously [2,7].

2.5. Two-bottle choice (TBC) paradigm

To evaluate the voluntary consumption of morphine using a TBC paradigm, each rat offspring was housed individually in cages after testing of SPT with two bottles for a period of 12 days of testing (PND 39-50) [2,7,9]. In one bottle, morphine sulfate was dissolved in 3% sucrose solution and also 3% sucrose solution was in control bottle as follow; on days 1–4 (0.3 mg/ml morphine); 5–8 (0.5 mg/ml morphine) and 9–12 of test (0.7 mg/ml morphine). Rats were allowed continuous access to both bottles. To minimize effects related to learning, the position of the bottles in the cage was changed at the time of daily bottle weighing. Fluid intake was measured by weighing the bottles between 9:00 and 10:00 am daily. Body weights of the rat offspring were measured in the start of each period. The average morphine and water consumption, and preference ratios (ml morphine solution consumed/total ml consumed), were evaluated during each 4-day period.

2.6. Statistical analysis

The data were expressed as the mean ± SEM and analyzed using three-way analyses of variance (ANOVA) with the fixed factors treatment (saline or morphine) × exercise (no swim or swim) × sex (male or female) and with repeated measures as required. Post-hoc analyses were carried out using Tukey's test. Statistical differences were considered significant at $P < 0.05$.

3. Result

3.1. Anxiety-like behavior

The results of the EPM testing in the pubertal male and female rat offspring born from morphine-dependent mothers are shown in Fig. 2. Three-way ANOVA in the percentage of time spent in the open arms in the pubertal male and female rat offspring born from morphine-dependent mothers revealed a significant effect of treatment

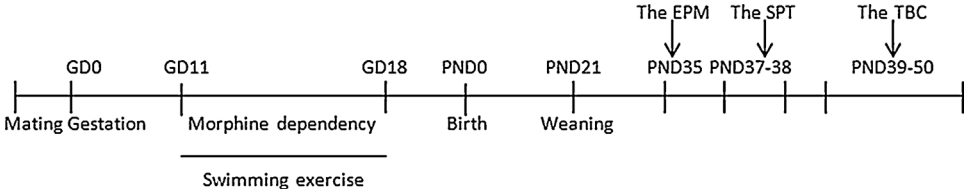

Fig. 1. Timeline of experiment (see Section 2 for details).

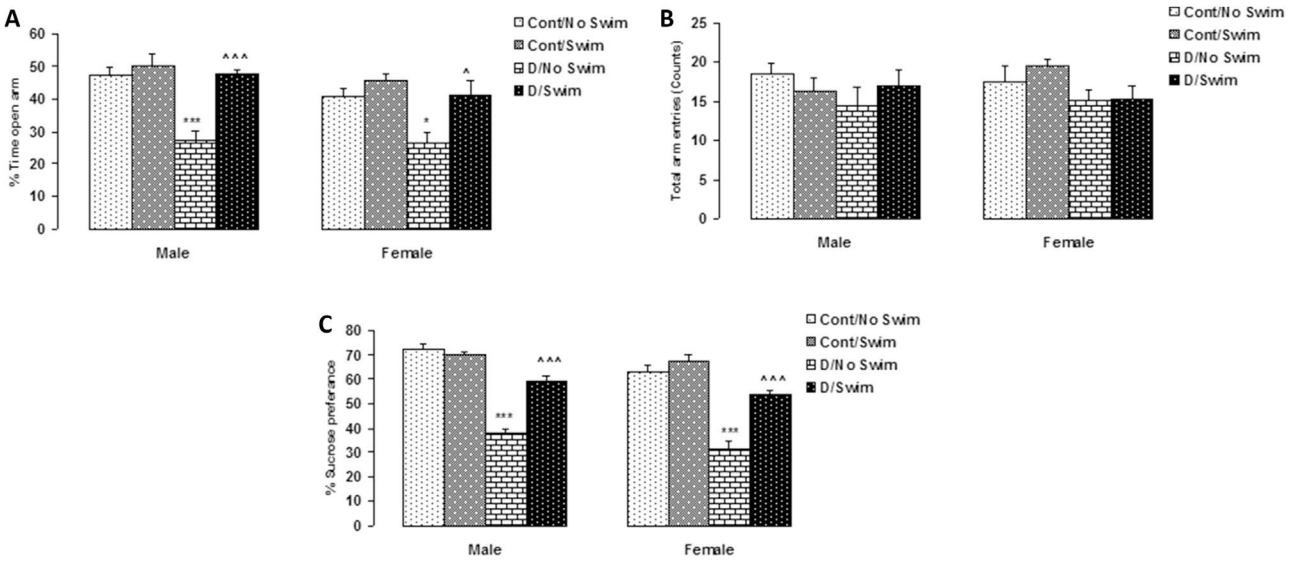

Fig. 2. Effect of regular swimming exercise on the anxiety/depressive -like behavior in the pubertal male and female rat offspring born from morphine-dependent mothers. A) The percentage of time spent in the open arms of the EPM. B) Total arms entries of the EPM. C) The percentage of sucrose preference using the SPT. The pubertal male and female rat offspring born from the D/Swim mothers spent significantly more time in the open arms than the D/No swim offspring. The D/No swim group offspring in both sexes spent significantly less time in the open arms than the Con/No swim group offspring. The male and female rat offspring born from the D/Swim mothers had a higher percentage of sucrose preference. In A) $^{***}P = 0.0001$, vs. Cont/No swim offspring. $^{\wedge\wedge\wedge}P = 0.0001$, vs. D/No swim offspring. In C) $^{***}P = 0.0001$, vs. Cont/No swim offspring and $^{\wedge\wedge\wedge}P = 0.0001$, vs. D/No swim offspring.

($F_{1,56} = 22.95$, $P = 0.0001$), and exercise ($F_{1,56} = 25.147$, $P = 0.0001$), sex ($F_{1,56} = 4.183$, $P = 0.046$), and treatment × exercise ($F_{1,56} = 9.89$, $P = 0.003$), and treatment × exercise × sex ($F_{1,56} = 2.76$, $P = 0.036$) interactions. Between-group comparisons indicated that the percentage of time spent in the open arms of the pubertal male and female rat offspring born from the sedentary morphine-dependent mothers (D/No Swim) were significantly lower than their sedentary control mothers (Cont/No Swim) (male: $P = 0.0001$; female: $P = 0.017$ respectively). Whereas the percentage of time spent in the open arms of the offspring born from the swimmer morphine-dependent (D/Swim) mothers were significantly higher than their control mothers (D/No Swim) (male: $P = 0.0001$; female: $P = 0.012$, respectively) (Fig. 2A). Also, there were no significant difference in treatment, exercise, and sex effects and interaction among them in total arms entries using a three-way ANOVA in the pubertal male and female rat offspring born from morphine-dependent mothers (Fig. 2B).

3.2. Depression-like behavior

The results of the SPT testing in the pubertal male and female rat offspring born from morphine-dependent mothers are shown in Fig. 2C. Three-way ANOVA in the percentage of sucrose preference revealed a significant effect of treatment ($F_{1,56} = 185.24$, $P = 0.0001$), exercise ($F_{1,56} = 44.59$, $P = 0.0001$) and sex ($F_{1,56} = 12.14$, $P = 0.001$), also treatment × exercise ($F_{1,56} = 38.74$, $P = 0.0001$) and treatment × exercise × sex ($F_{1,56} = 10.21$, $P = 0.0001$) interactions. Between-group comparisons indicated that sucrose preference of the male and female offspring born from the sedentary morphine-dependent mothers (D/No Swim) were significantly less than Cont/No swim group (both, $P = 0.0001$), while it was significantly more in male and female offspring (both, $P = 0.0001$) born from swimmer morphine-dependent mothers (D/Swim).

3.3. Assessment of voluntary morphine consumption

The results of the voluntary morphine consumption and morphine preference ratio during three period of TBC test in the pubertal male and female rat offspring born from morphine-dependent mothers are shown in Figs. 3 and 4. Three -way ANOVA with repeated measure (day) for morphine consumption during three period of intake revealed a significant effect of day ($F_{2,112} = 49.62$, $P = 0.0001$), treatment ($F_{1,56} = 365.69$, $P = 0.0001$), exercise ($F_{1,56} = 54.34$, $P = 0.0001$), sex ($F_{1,56} = 0.42$, $P = 0.51$), treatment × exercise × sex ($F_{4,56} = 14.95$, $P = 0.0001$), and day × treatment × exercise × sex ($F_{8,112} = 8.68$, $P = 0.0001$) interactions. Between-group comparisons indicated that morphine consumption during three period of TBC test is increased significantly in the male and female offspring born of morphine-dependent (D/No swim) mothers compared to the Cont/No swim group mothers (male & female: $P = 0.0001$, for each of three periods). Also, it was significantly less during the each of three periods in the male and female offspring born from the swimming morphine-dependent mothers (D/Swim) compared to the offspring born from sedentary morphine-dependent mothers (D/No swim) (male: $P = 0.037$, $P = 0.0001$, $P = 0.0001$, respectively, female: $P = 0.001$, $P = 0.0001$, $P = 0.0001$, respectively).

Three -way ANOVA with repeated measure (day) for morphine preference ratio during three period of intake revealed a significant effect of day ($F_{2,112} = 31.78$, $P = 0.0001$), treatment ($F_{1,56} = 341.87$, $P = 0.0001$), exercise ($F_{1,56} = 45.82$, $P = 0.0001$), sex ($F_{1,56} = 0.95$, $P = 0.33$), treatment × exercise × sex ($F_{4,56} = 13.07$, $P = 0.0001$), and day × treatment × exercise × sex ($F_{8,112} = 2$, $P = 0.05$) interactions. Between groups comparisons showed that morphine preference ratio during three period of test were higher in male ($P = 0.0001$, for each of three periods) and female ($P = 0.0001$, for each of three periods) offspring born from the sedentary morphine-dependent mothers (D/No swim) than Cont/No swim group. While, it was significantly less during three period of test in male ($P = 0.002$, $P = 0.0001$, $P = 0.0001$, respectively) and female ($P = 0.001$, $P = 0.0001$, $P = 0.0001$, respectively) offspring born from swimmer morphine-dependent mothers (D/Swim) than D/No swim group. Also, there were no significant changes in day, treatment, exercise, and sex effects and interaction among them in water consumption using a three-way ANOVA with repeated measure in the pubertal male and female rat offspring born from morphine-dependent mothers (Figs. 3 B and 4 B).

4. Discussion

This study has shown that the development of morphine dependence in the sedentary rat mothers on gestational days 11–18 exhibited anxiety/depressive-like behaviors and voluntary consumption of

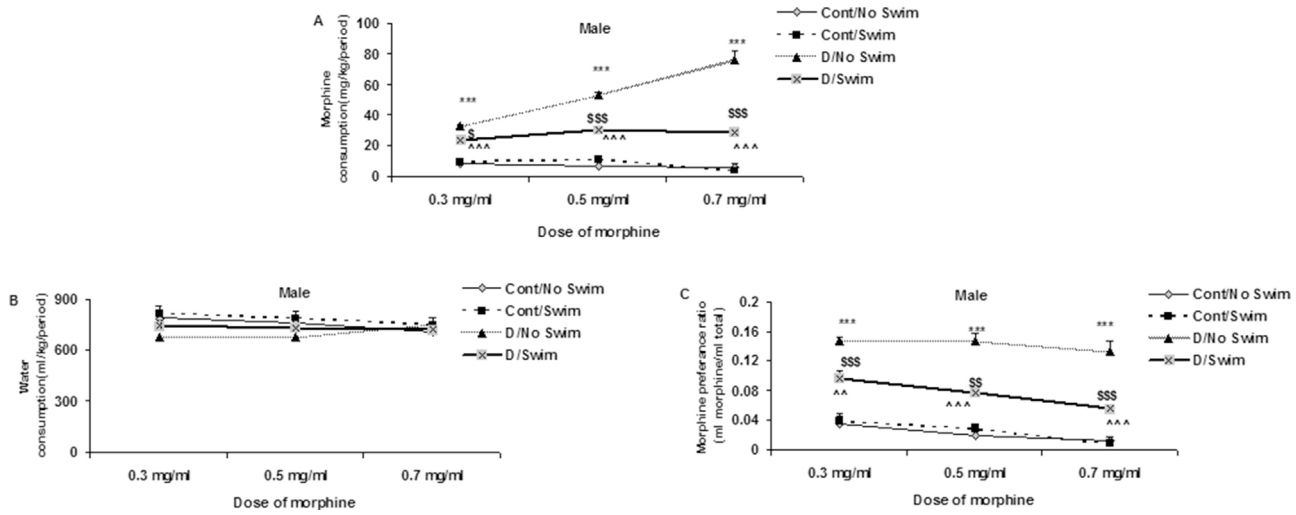

Fig. 3. Effect of regular swimming exercise on voluntary morphine consumption in the pubertal male rat offspring born from morphine-dependent mothers using TBC paradigm. A) Morphine consumption. B) Water intake. C) The morphine preference ratio. Rat offspring born from the D/No swim mothers showed a higher consumption and preference ratio compared with the Cont/No swim group during three periods of intake, while they were lower in D/swim offspring. In A and C) $^{***}P = 0.0001$, vs. Cont/No swim offspring. In A and C) $^{\$}P = 0.037$, $^{\$\$}P = 0.002$, $^{\$\$\$}P = 0.0001$, vs. D/No swim offspring. In A and C) $^{\wedge}P = 0.004$, $^{\wedge\wedge}P = 0.0001$ vs. Cont/swim offspring.

morphine in the pubertal male and female rat offspring which is consistent with our previous results [9]. These results could be due to increased sensitivity this period in the development of brain circuits that sensitized the pubertal male and female rat offspring to the rewarding effect of morphine. Also, prenatal morphine exposure can cause long-term changes in μ-opioid receptor densities in the nucleus accumbens and amygdale involved in rewarded and motivated behaviors [22]. Our findings demonstrated that a period of 8 days swimming exercise in morphine-dependent mothers during pregnancy decreased anxiety/depressive-like behaviors and also oral morphine preference in their pubertal offspring of both sexes. This finding is supported further by our previous study showing that 21 days of voluntary exercise during pregnancy in morphine-dependent mothers decreases anxiety-like behavior and voluntary morphine consumption in male rat offspring [9]. Also, previous studies have confirmed that swimming exercise decreased morphine-induced CPP in both sexes and behavioral sensitization in male offspring following maternal separation [1], depression [19], the severity of psychological dependence and voluntary drug consumption in the methamphetamine [6] and morphine [7]-withdrawn rats. It seems that exercise could decrease the rewarding effects of morphine probably by recruiting a common brain pathway [20] which can be attributed to the attenuation of voluntary morphine consumption in this study. Also, our results showed that prenatal morphine exposure had probably the same effects on the developing brain circuits in offspring of both sexes.

We have found that swimming exercise has not decreased anxiety/depressive-like behaviors in the control-swimming exercise group (non-dependent rats). It seems that drug non-dependent rats must swim more than 8 days for reducing anxiety and depression, as verified by our previous studies [6,7].

Based on the literature, we could assume that the antidepressant and anti-anxiety effects of exercise in offspring born from swimmer morphine-dependent mothers in present study may be due to an increase in the galanin expression in noradrenergic locus coeruleus that may contribute to the stress-protective effects of exercise [18], activation of opioidergic pathways [14], antioxidant activity [13], brain-

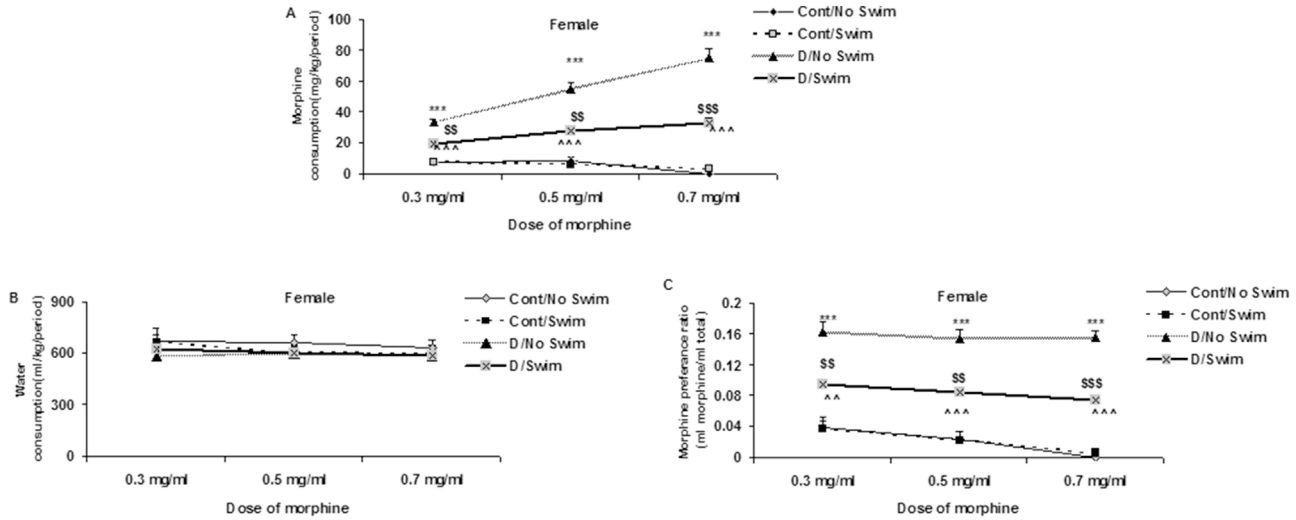

Fig. 4. Effect of regular swimming exercise on voluntary morphine consumption in the pubertal female rat offspring born from morphine-dependent mothers using TBC paradigm. A) Morphine consumption. B) Water intake. C) The morphine preference ratio. Rat offspring born from the D/No swim mothers showed a higher consumption and preference ratio compared with the Cont/No swim offspring during three periods of intake. While, D/swim rat offspring had a lower voluntary consumption of morphine. In A and C) $^{***}P = 0.0001$, vs. Cont/No swim offspring. In A and B) $^{\$\$}P = 0.001$, $^{\$\$\$}P = 0.0001$, vs. D/No swim offspring. In A and C) $^{\wedge}P = 0.004$, $^{\wedge\wedge}P = 0.001$, $^{\wedge\wedge\wedge}P = 0.0001$, vs. Cont/swim offspring.

derived neurotrophic factor (BDNF) [11] and decrease of corticosterone levels [21]. Thus, increased BDNF, galanin and antioxidant parameters in swimming mothers can be transmitted to the developing fetus, that may play an important role in neurogenesis and the neuronal plasticity of the central nervous system [11], the reduction of anxiety [21] and depression [8]. Future studies need to examine the neurobiological mechanisms.

5. Conclusion

This study provides novel evidence that swimming exercise in pregnant rat mothers during the development of morphine dependence decreased anxiety/depressive-like behaviors and voluntary consumption of morphine in the pubertal male and female offspring. Our findings could be exploited in the development of therapeutic approaches in the prevention of prenatally morphine-induced behavioral sensitization after first postnatal morphine exposure.

Conflict of interest

The authors report no conflicts of interest.

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